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The role of oral (methyl)ergometrine in the prevention of postpartum haemorrhage

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Abstract

Postpartum haemorrhage (PPH) is one of the most important causes of maternal mortality in developing countries. A consensus was reached on active management of the third stage of labour for all parturients especially for those for whom the access to hospital services is difficult or time-consuming. Oral (methyl)ergometrine was considered to be a possible alternative prophylactic oxytocic, that was easy to administer and suitable to be used in developing countries. A research project was set up to investigate its suitability to be used for active management of the third stage of labour. It was examined on its stability under tropical conditions; on its pharmacokinetic and pharmacodynamic properties and on its clinical effect on the amount of bloodloss after childbirth. Oral (methyl)ergometrine is unstable even when stored after refrigerated conditions. Its pharmacokinetic and dynamic properties are unpredictable and no clinical effect on reduction of bloodloss after childbirth has been shown. To ameliorate a product's stability seems unlogical, if the same product shows unfavourable pharmacokinetics. All the more so, since the tablets do not show the wanted clinical effects. Oral (methyl)ergometrine is not an alternative to parenteral prophylactic oxytocic drugs in the active management of the third stage of labour.

Keywords: Prevention of PPH; Oral (methyl)ergometrine; Stability; Pharmacokinetics and pharmacodynamics; Clinical effect

1. Introduction

1.1. Maternal mortality

Every four hours, day in, day out, a jumbo jet crashes and all on board are killed. The 250 passengers are all women. They are all either pregnant or have recently given birth to a child.

This shocking statement was given by Malcolm Potts at the World Health Organization's (WHO) interregional Meeting on the prevention of maternal mortality, November 1985 [1]. This statement is all the more intolerable because most of these deaths are theoretically preventable with present knowledge and equipment.

Worldwide at least half a million women die annually from causes related to pregnancy and childbirth. All but 6000 occur in developing countries, where 86% of the world's births take place [2]. It shows the poignant

inequality in maternal health between the rich and the poor. One of the most important causes of maternal mortality is obstetric haemorrhage, claiming 150 000 lives annually [3].

1.2. Postpartum haemorrhage

Postpartum haemorrhage (PPH), defined by the WHO [2] as postpartum bloodloss ≥ 500 ml is a clinical diagnosis that encompasses excessive bloodloss after delivery and, if untreated, may result in shock and death of the mother. The choice of 500 ml is arbitrary but is a loss that most mothers can tolerate without risk. In countries where many women have severe anaemia, maternal bloodloss of even 250 ml may be fatal [4]. Another reason for the 500 ml criterion is that bloodloss is often underestimated: accurately measured loss is usually about twice the estimated loss.

The clinical consequences of postpartum bloodloss depend on both the amount and rate of bloodloss and whether the mother's health is good, a factor partly included in the definition of PPH.

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1.3. Primary prevention of PPH

Primary prevention includes the prophylactic treatment of those women at high risk for PPH. However, women at low risk for PPH are not excluded from excessive loss of blood after delivery. If a woman's immediate referral to hospital is logistically impracticable, as is the case in many third world countries, preventive measures against PPH are required for all women, not only for those at high risk for PPH. Therefore, primary prevention of PPH is advocated at all levels of obstetric care.

Primary prevention of PPH implies active management of the third stage of labour. Active management includes use of an oxytocic, early cord clamping, and active expulsion of the placenta. The oxytocic drug of choice is oxytocin, 10 IU, given intramuscularly [5].

Evidence for the effectiveness of active management of the third stage in women at low risk for PPH is still not conclusive. Whether women delivering at home with easy accessibility to hospital or those at low risk delivering in hospital should have active management of the third stage of labour remains controversial and awaits support until a clinical trial in this particular group of women has shown the effectiveness of active management (a modification on the WHO-consensus, 1989 [6]). Guidelines for clinical practice are shown in the flow chart (Fig. 1).

1.4. WHO-consensus: active management of third stage for all [6]

A Technical Working Group on the prevention and management of postpartum haemorrhage was convened by WHO in Geneva, 3–6 July 1989. A consensus was reached on primary preventive measurements of PPH for all parturients, consisting of active management of the third stage of labour in particular for those with a difficult or time-consuming access to hospital services. This implies active management of the third stage of

labour. It is also being recommended at the first, most peripheral, levels of obstetric care which have difficult access to hospital services.

The major drawback was to find a prophylactic oxytocic that was easy to administer and stable [6]. During the working group, one of the midwives, Barbara Kwast, suggested giving oral ergometrine. From that day on the project on oral ergometrine was initiated.

2. Study design

2.1. Oral (methyl)ergometrine as an easy alternative for oxytocin intramuscularly in active management of the third stage of labour?

The research project consisted of three studies, oriented toward the following questions:

- Is oral (methyl)ergometrine in contrast to intravenous (methyl)ergometrine stable under tropical conditions? (Stability study)
- Are the pharmacokinetic and pharmacodynamic properties of (methyl)ergometrine tablets favourable enough for use in the third stage of labour? (Pharmacological study)
- Do ergometrine tablets have a clinical effect on bloodloss after childbirth, in spite of the answers on the questions mentioned above? (Clinical trial)

The three questions are related, but were answered independently. Assuming that the pharmacological study and clinical trial would lead to positive results, the stability study was started first as there was doubt about the stability of the tablets under tropical conditions. While this stability study was being set up and started, the pharmacological and clinical parts of the project were started simultaneously. This set up of the research project had been chosen to underline the three-fold question, each related to the completely different grounds for which an answer had to be given before an answer could be given to the principle question: "Is oral (methyl)ergometrine a suitable alternative prophylactic drug to prevent postpartum haemorrhage?". Such an approach to the question would also detect which aspect (stability, pharmacological or clinical) needs amelioration.

3. Results

3.1. Stability under simulated tropical conditions [7,8]

The stability of oral preparations of the two ergometrine compounds methylergometrine and ergometrine under tropical conditions was unknown. *Stability* is defined as the ability of a drug to retain its

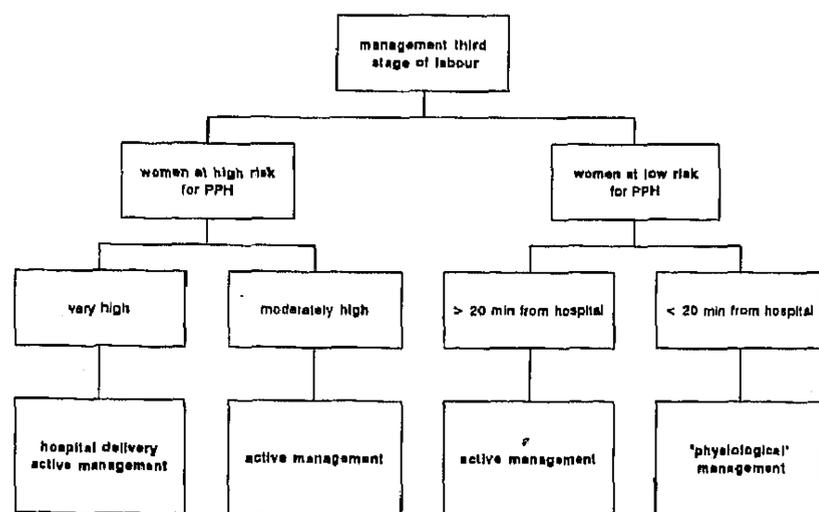


Fig. 1. Flowchart illustrating guidelines for clinical practice of postpartum haemorrhage.

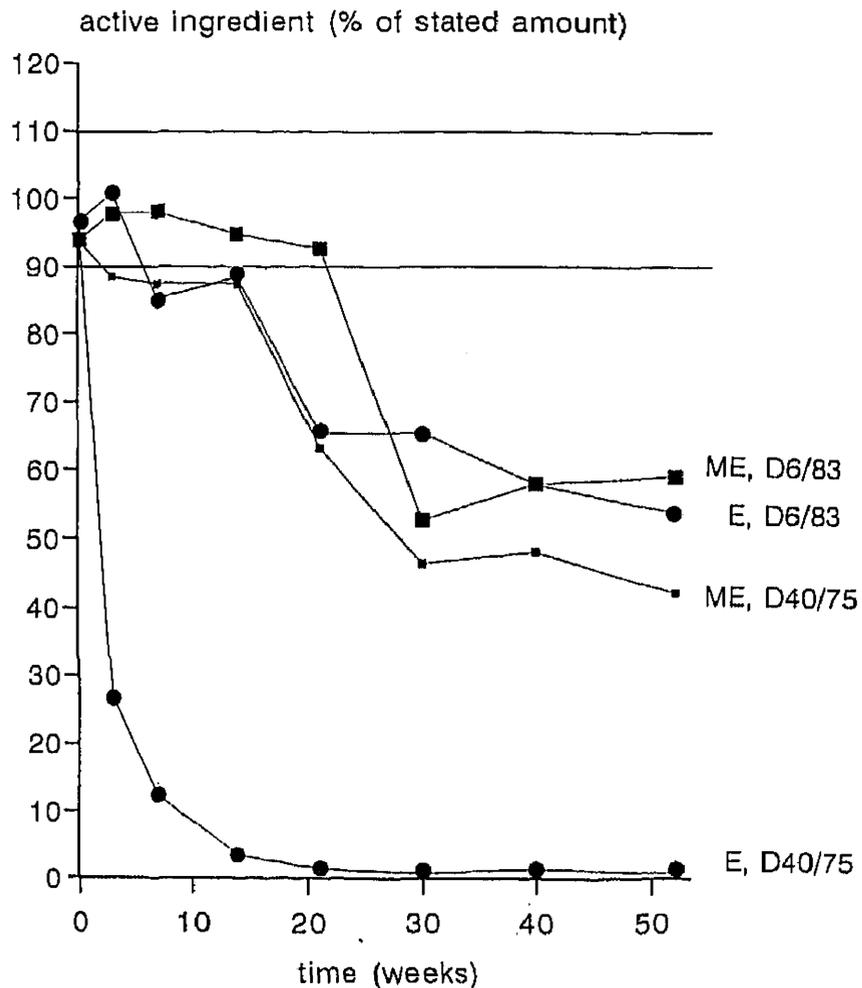


Fig. 2. Stability of oral ergometrine and methylergometrine exposed to least (D6/83) and most (D40/75) extreme conditions; E, ergometrine; ME, methylergometrine; D6/83, 6°C, 83% relative humidity (RH) and darkness; D40/75, 40°C, 75% RH and darkness.

properties within specified limits throughout its shelf-life. For (methyl)ergometrine the active ingredient should be in between 90 and 110% of the stated amount. *Shelf-life* is the period of time during which a drug product is expected, if stored correctly, to remain within specifications as determined by stability studies. The shelf-life is used to establish the expiry date of each batch.

The 'shelf lives' of ergometrine and methylergometrine tablets were examined by exposing these to seven artificially controlled conditions. Samples were analyzed by high performance liquid chromatography (HPLC) at nine different sampling times over a period of 1 year to determine the content of ergometrine and methylergometrine. Under refrigerated storage (dark 6°C/83% relative humidity; D6/83), less than 90% of the stated amount of active ingredient was found in the ergometrine tablets after 14 weeks and in methylergometrine tablets after 21 weeks. When stored in the dark at 40°C with 75% relative humidity (D40/75), the tablets fell below accepted specification criteria (90–110% of stated amount of active ingredient) within 3 weeks for ergometrine and 21 weeks for the coated methylergometrine tablets (Fig. 2).

The stability of uncoated ergometrine was far less than that of coated methylergometrine tablets. Insta-

bility worsened under extreme humid and hot conditions, for both ergometrine and methylergometrine. From week 31 onwards, the coating did not seem to protect the compound anymore, irrespective of the condition of exposure.

Tropical conditions make the tablets unstable with humidity as the main adverse factor. Under all simulated conditions, both ergometrine and methylergometrine tablets were unstable.

3.2. Pharmacokinetics and bioavailability

Ergometrine and methylergometrine belong to the group of oxytocic drugs which enhance uterine motility. As mentioned earlier prophylactic use of such drugs in the third stage of labour reduces the risk of PPH and the need for further oxytocic therapy in the puerperium. Because pharmacokinetic data for ergometrine and methylergometrine were scarce [9,10] and mainly concerned methylergometrine [11,12], male volunteers were first studied to determine the pharmacokinetics for the oral administration of ergometrine. As the pharmacokinetic data of ergometrine in male volunteers showed a large variation in bioavailability [13], a comparable study was performed for methylergometrine in both men and (non-pregnant) women to investigate and compare the results with the previous data. Thus, three series of experiments were performed.

The aim of these experiments was to assess the pharmacokinetics and bioavailability of comparable doses methylergometrine and ergometrine (parallel design) in six male volunteers after an intravenous dose and an oral dose of the maleate (cross-over design) [14]. Further, the pharmacokinetics and bioavailability of methylergometrine in six non-pregnant women were assessed and compared with the methylergometrine values in men (parallel design in gender) [15].

Fig. 3 shows the methylergometrine plasma concentrations (ng/ml) versus time after intravenous and oral administrations in one representative male volunteer. After *intravenous administration*, the pharmacokinetic profile of methylergometrine can be described by a two-compartment model. After *oral administration*, the pharmacokinetic profile can be described with a one-compartment model. After oral administration the compound is rapidly absorbed after a lag time of 10 min. A maximum plasma concentration of 0.67 ng ml⁻¹ was reached after 24 min and the half-life (2.7 h) was not significantly different from the half-life after intravenous administration (2.31 h).

Table 1 gives the mean pharmacokinetic parameters of methylergometrine maleate after intravenous and oral administrations in six male volunteers. This shows an extreme interindividual variation in bioavailability (and $T_{1/2abs}$). The same interindividual

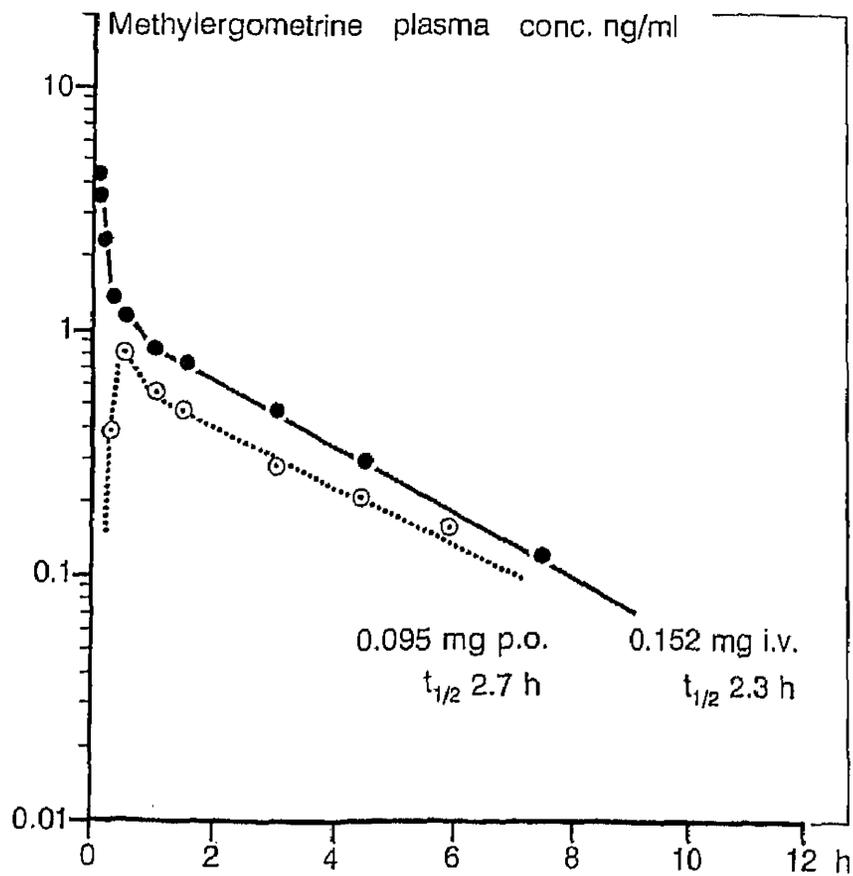


Fig. 3. Methylergometrine plasma concentrations (ng/ml) versus time curves after oral administration of 0.125 mg methylergometrine maleate (0.095 mg free base) and after intravenous administration of 0.200 mg methylergometrine maleate (0.152 mg free base) in one representative male subject. p.o., per os; i.v., intravenous.

variation was shown in experiments with methylergometrine in non-pregnant women [15] and with ergometrine in men [13].

The experiments with oral administrations for both men and women show a large inter-individual variability in bioavailability. From a pharmacokinetic point of view, the oral route of administration does not seem the most reliable way for accurate dosing to prevent post-partum haemorrhage.

Table 1

Mean pharmacokinetic parameters of methylergometrine after an intravenous and oral dose of methylergometrine in six male volunteers ($n = 6$)

	Intravenous	Oral	%CV	P
Dose (μg)	152	95		
$T_{1/2\beta}$ (h)	1.85 (0.28)	2.08 (0.43)		0.31
CL (l/h)	32.2 (11.8)	31.1 (10.3)		0.50
V_{ss} (l)	71.5 (25.9)	94.4 (38.9)		0.11
Bioavailability (%)		84.9 (37.2)	44	
$T_{1/2\text{abs}}$ (h)		0.08 (0.08)	100	
MAT		0.87 (0.72)	83	

T_{lag} , lag-time; $T_{1/2\beta}$ (h), the half-life of elimination, calculated by least-square linear regression analysis; C_L (l/h), total body clearance = $\text{Dose}/\text{AUC}_{0-\infty}$; V_{ss} (L), the volume of distribution in steady state ($V_{ss} = \text{Dose} \cdot \text{AUMC}_{0-\infty} / \text{AUC}_{0-\infty}^2$); Bioavailability, $\text{AUC}_{\text{oral}} \cdot \text{Dose}_{\text{i.v.}} / \text{AUC}_{\text{i.v.}} \cdot \text{Dose}_{\text{oral}}$; $T_{1/2\text{abs}}$ (h), the half-life of absorption, calculated by least-square linear regression analysis; MRT, the mean residence time AUMC/AUC after oral administration; MAT, the mean absorption time ($\text{MRT}_{\text{po}} - T_{\text{lag}}$)

3.3. Pharmacodynamics [16]

The objective was to study the pharmacodynamic and pharmacokinetic effect of oral and intravenous methylergometrine upon uterine motility during menstruation. Intra-uterine pressure (IUP) was measured in six volunteers with a fluid-filled sponge-tipped catheter during menstruation. Methylergometrine maleate was given orally (0.5 mg) or intravenously (0.2 mg) in a cross-over design.

After intravenous administration, a fast increase of the frequency of uterine contractions and basal tone occurred with a decrease of amplitude, lasting at least 30 min. Oral administration had a longer latency time and a less marked effect on uterine motility. Pharmacokinetic data, such as the maximum plasma concentration (C_{max}), the time at which C_{max} is reached (t_{max}), and the half-life of absorption ($T_{1/2\text{abs}}$) also showed large individual variation after oral administration (Fig. 4).

Oral administration of methylergometrine had an unpredictable and a late effect on uterine motility in the menstruating uterus probably due to an unpredictable bioavailability in contrast with the fast and predictable effect after intravenous administration.

The effects of an intravenous dose of methylergometrine on IUP *without* and *with* preceding oral methylergometrine maleate (0.5mg) 24 h before are strikingly different (Fig. 5). A strongly diminished effect of intravenous administered methylergometrine maleate 24 h after oral administration suggests a long-lasting receptor blockade. It seemed as if the uterus was insensitive to the methylergometrine maleate-dose. The first dose may affect and change the uterine receptors for methylergometrine maleate. Methylergometrine maleate probably blocks α -receptors in the inner layer, specifically affecting the basal tone of this layer [17–19].

3.4. Clinical effects

Active management with oral ergometrine maleate 0.4 mg was compared with expectant management for the control of bloodloss in the third stage of labour in women at low risk for PPH.

The design of the study was a three-arm randomized trial in which 0.4 mg ergometrine maleate (2 tablets of 0.2 mg) was set off against placebo, and both groups were compared with a standard oxytocin regimen of 5 IU.

It was calculated that a sample size of 140 per group was required to show a clinically relevant 30% reduction of bloodloss with an error rate of 0.05 (two-sided) and a power of 0.80. To allow comparison with the standard prophylactic regimen, a third group receiving intramuscular oxytocin was added. Formal randomisation was conducted in a 2:2:1 design.

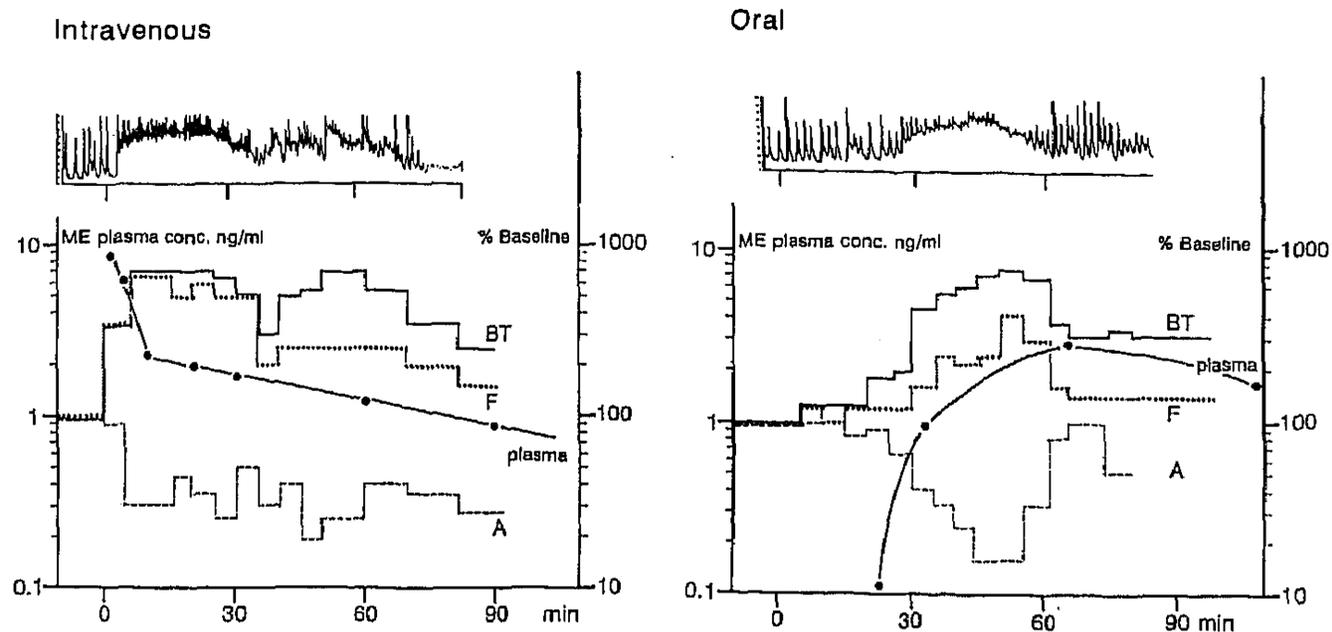


Fig. 4. Effect of methylergometrine maleate (ME) after intravenous (0.2 mg) [left] and oral (0.5 mg) [right] administration in one volunteer. At $t = 0$, ME was administered. *Top-trace*: Effect on intra-uterine pressure. *Bottom-trace*: Effect on frequency (F), basal tone (BT) and amplitude (A). The mean values of F, B and A during 30 min before drug administration were regarded as baseline values and set at 100%, the increase in a 5 min period was expressed as a percentage of baseline value and plotted versus time after intravenous (0.2 mg) ME and oral (0.5 mg) ME administrations.

Of 367 parturients, 146 were randomized to ergometrine maleate 0.4 mg, 143 to the placebo and 78 to intramuscular oxytocin. Compared with placebo, ergometrine reduced bloodloss by 5% (-5% ; confidence interval (CI): $-20 - +13\%$) and oxytocin (-9% ; CI: $-26 - +12\%$). Fig. 6 shows the estimates for the effect of the treatments on the amount of bloodloss.

4. Conclusions

Oral ergometrine has too little effect on bloodloss after childbirth in order to be a good alternative to parenteral prophylactic management.

Oral (methyl)ergometrine is not an alternative to parenteral prophylactic oxytocic drugs in the active

management of the third stage of labour. It is instable, its pharmacokinetic and pharmacodynamic properties are unpredictable and no clinical effect has been shown. All in all, the negative outcomes of the three studies on oral (methyl)ergometrine strengthen each other. To ameliorate a product's stability seems unlogical, if the same product shows unfavourable pharmacokinetics. Even more so, because tablets do not show clinical effects. The research quest for easy alternatives, therefore, should be continued. If not, maternal mortality will remain a huge problem, costing 1500 lives a day.

The conclusion drawn from our research project is two-fold:

- There is still no easy alternative to intramuscular oxytocin for the active management of the third stage of labour.

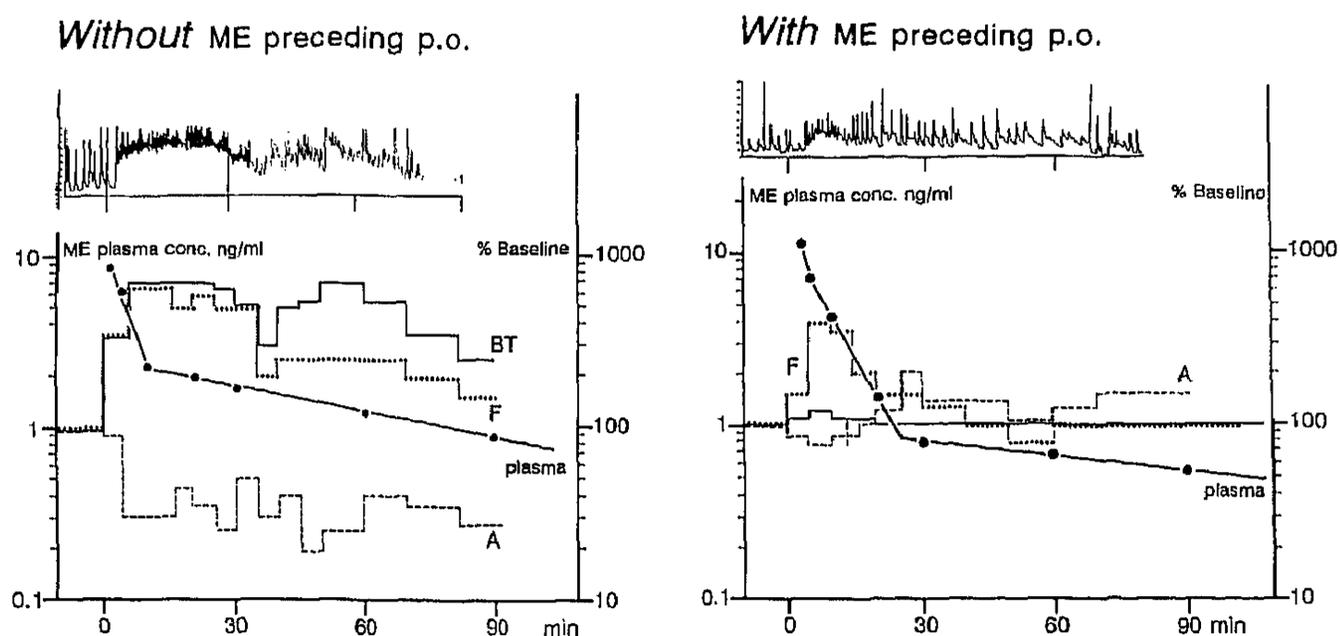


Fig. 5. Effect of methylergometrine maleate (ME) after intravenous (0.2 mg) administration *without* preceding oral ME [left] and *with* preceding oral ME (0.5mg) [right] in one volunteer. At $t = 0$, ME was administered. For explanation of tracings, see Fig. 4.

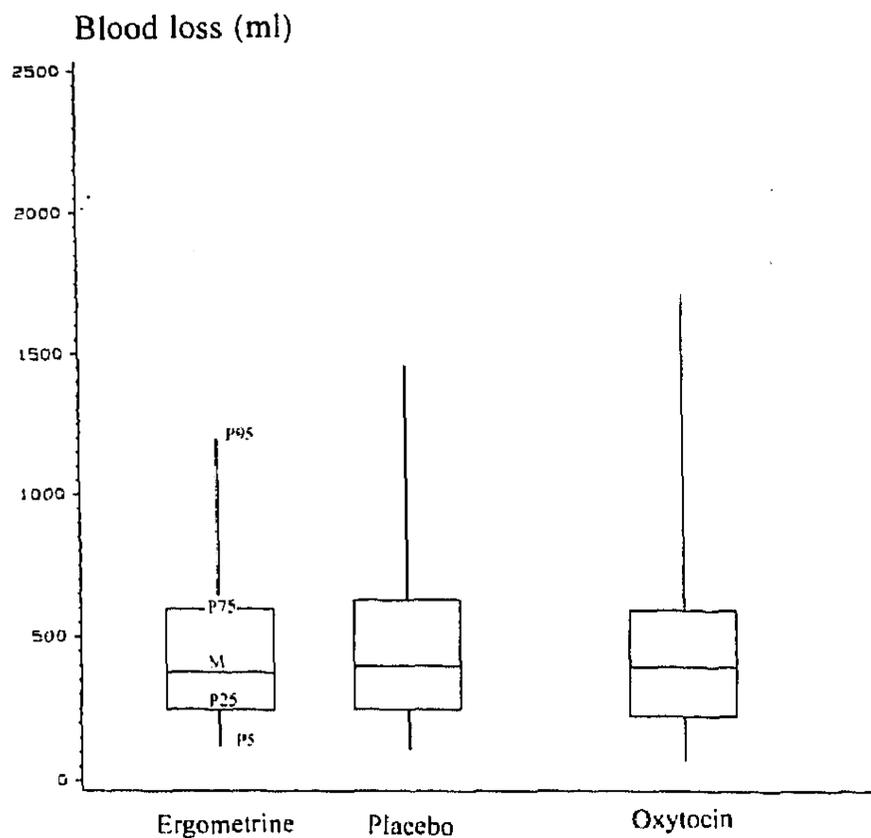


Fig. 6. Effect of treatment on the amount of bloodloss postpartum (ml). Abbreviations: M, median; P, percentile (box-plot).

– Because of unfavourable pharmaceutical and pharmacokinetic properties oral (methyl)ergometrine should be excluded from the medication list.

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